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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/314,161	05/19/1999	MICHAL EISENBACH-SCHWARTZ	EIS-SCHWARTZ	4767

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EXAMINER
BUNNER, BRIDGET E

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/314,161	Applicant(s) EISENBACH-SCHWARTZ ET AL.	
	Examiner Bridget E. Bunner	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,19 and 38-46* is/are pending in the application.

4a) Of the above claim(s) *3,9-16,42 and 44-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-8,19,38-41 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-16, 19, 38-46* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 30 December 2002 (Paper No. 20) has been entered in full. Claims 1-15, 19, and 38 are amended, claims 17-18, and 20-37 are cancelled, and claims 41-46 are added. The declaration of 30 December 2002 (Paper No. 19), filed under 37 CFR 1.132, has been considered by the Examiner.

Newly submitted claims 42 and 44-46 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claim 42 further limits the method of claim 1 by indicating an individual is suffering from a disease. However, in Applicant's response of 14 September 2001 (Paper No. 14), Applicant elected with traverse the species of "injury" as the type of defect suffered by the individual, rather than "disease". Therefore, since claim 42 does not read upon "injury", the claim is withdrawn. Furthermore, claims 44-46 are withdrawn because these claims do not read upon the elected invention. Claims 44-46 recite the administration of peptides, antigens, or nucleotide sequences. However, Applicant elected Group I, administration of NS-specific activated T cells, with traverse in the response of 25 April 2001 (Paper No. 12).

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 42 and 44-46 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. It is noted that claims 3 and 9-16 were previously withdrawn from consideration in the Office Actions of 05

December 2001 (Paper No. 15) and 30 July 2002 (Paper No. 17). Claims 3 and 9-16 are drawn to nonelected species and inventions.

Applicant's continued traversal of the Restriction requirements set forth in Paper No. 13 (14 June 2001) and Paper No. 9 (28 February 2001), especially regarding Groups I-III, appears moot since the restriction requirement was made final in the Office Action of 05 December 2001 (Paper No. 15). If Applicant wishes to pursue the matter further, a petition should be filed in accordance with 37 CFR 1.144.

Claims 1-2, 4-8, 19, 38-41, and 43 are under consideration in the instant application, as they read upon NS-specific activated T cells and injury.

Withdrawn Objections and/or Rejections

1. The rejection of claims 1-2, 4-8, 19, and 38-40 under 35 U.S.C. § 112, first paragraph (enablement) as set forth at pg 4-9 of the previous Office Action (Paper No. 17, 30 July 2002) and pg 6-9 of the Office Action of 05 December 2001 (Paper No. 15) is *withdrawn in part* in view of the claim amendments of 30 December 2002 (Paper No. 20), regarding the type of administration and "preventing or inhibiting neuronal degeneration". Please see section below on 35 U.S.C. § 112, first paragraph.

2. The rejection of claims 38-39 under 35 U.S.C. § 112, second paragraph as set forth at pg 9 of the previous Office Action (Paper No. 17, 30 July 2002) is *withdrawn* in view of Applicant's persuasive arguments (Paper No. 20, 30 December 2002). Please see section below on 35 U.S.C. § 112, second paragraph.

3. The rejection of claims 1, 4-6, 8, and 38-40 under 35 U.S.C. § 102(b) as set forth at pg 9-10 of the previous Office Action (Paper No. 17, 30 July 2002) and pg 11 of the Office Action of

05 December 2001 (Paper No. 15) is *withdrawn* in view of the claim amendments of 30 December 2002 (Paper No. 20).

4. The rejection of claim 19 under 35 U.S.C. § 103(a) as set forth at pg 11 of the previous Office Action (Paper No. 17, 30 July 2002) is *withdrawn* in view of the amended claims of 30 December 2002 (Paper No. 20).

Specification

5. The objections to the specification regarding a more descriptive title of the invention is maintained and held in abeyance until all other issues are resolved.

Claim Objections

6. The objection to claims 1, 2, 19, and 38-41 regarding the issue that the claims are not limited to the elected species is maintained and held in abeyance until allowable subject matter is identified. The basis for this rejection is set forth for claims 1, 2, and 19 at pg 4 of the Office Action of 05 December 2001 (Paper No. 15).

Double Patenting

7. The rejections of claims 1-2 and 38-41 and 43 under the judicially created doctrine of obviousness-type double is maintained and held in abeyance until all other issues are resolved. The basis for this rejection is set forth for claims 1-2 at pages 4-6 of the Office Action of 05 December 2001 (Paper No. 15).

Claim Rejections - 35 USC § 112

8. Claims 1-2, 4-8, 19, 38-41, and 43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (i) a method of reducing secondary neuronal degeneration in the central nervous system (CNS) or peripheral nervous system of an individual

suffering from the degenerative effects of spinal cord injury or blunt trauma comprising intraperitoneally administering to an individual in need thereof a composition consisting of activated T cells sensitized to myelin basic protein (MBP) wherein the MBP-activated T cells accumulate at the site of injury or blunt trauma to reduce secondary neuronal degeneration, does not reasonably provide enablement for a method of reducing neuronal degeneration in the central nervous system or peripheral nervous system of an individual suffering from an injury or disease involving neuronal degeneration, comprising administering to an individual in need thereof at least one active ingredient selected from the group consisting of NS-specific activate T cells, a NS-specific antigen, a peptide derived from a NS-specific antigen, a nucleotide sequence encoding a NS-specific antigen, and a nucleotide sequence encoding a peptide derived from a NS-specific antigen, thereby causing NS-specific activated T cells to accumulate at the site of injury and prevent or inhibit neuronal degeneration at that site, wherein when said active ingredient is NS-specific T cells, and said administration is intraperitoneal. The specification also does not reasonably provide enablement for a method for reducing neuronal degeneration in the central nervous system or peripheral nervous system of an individual suffering from neuronal degeneration, comprising causing nervous system-specific activated T cells to accumulate at the site of neuronal degeneration in the individual, thereby reducing neuronal degeneration at that site. Finally, the specification while enabling for a method of establishing a T cell bank for future use, comprising (a) obtaining T cells from a human individual who is not suffering from a spinal cord injury or blunt trauma involving neuronal degeneration, (b) activating said T cells against at least one CNS myelin-associated antigen, and (c) storing said activated T cells in a cell bank of T cells that have been activated against a CNS myelin-associated antigen, for future use

in the case that the individual from whom the T cells were originally obtained sustains a spinal cord injury or blunt trauma of the central nervous system involving neuronal degeneration, does not reasonably provide enablement for a method for providing T cells for future use, comprising (a) obtaining T cells from a human individual who is not suffering from an injury or disease involving neuronal degeneration, (b) activating said T cells against at least one nervous system antigen, (c) storing said activated T cells in a cell bank of T cells that have been activated against a nervous system antigen, for future use in the case that the individual from whom the T cells were originally obtained sustains an injury or contracts a disease of the nervous system involving neuronal degeneration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The basis for this rejection is set forth for originally filed claims 1-2, 4-8, 16, and 19 at pg 6-9 of the Office Action of 05 December 2001 (Paper No. 15).

Applicant's arguments (Paper No. 20, 30 December 2002), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) At page 11 of the Response, Applicant asserts that the declaration of Prof. Michal Schwartz, filed under 37 CFR 1.132, sets forth experiments using another NS-specific antigen (other than MBP), which, when used to activate T cells, also has positive results as predicted in the present specification. Applicant contends that these experiments show that the active vaccination with Nogo-A peptide provides neuroprotection and that the corresponding passive administration of T cells directed against Nogo-A-derived peptide also provides neuroprotection. Applicant argues that thus, these experiments not only confirm statements in the present

specification that T cells activated by other NS-specific peptides will be neuroprotective, but also confirm that, if active vaccination provides neuroprotection, passive vaccination will also provide neuroprotection. Applicant submits that one of ordinary skill in the art would be able to conclude that T cells activated by any NS-specific antigen can also be operable for the reasons detailed in the specification and that no experimentation is invited.

Applicant's arguments have been fully considered but are not found to be persuasive. The declaration under 37 CFR 1.132 filed 30 December 2002 (Paper No. 19) is insufficient to overcome the rejection of claims 1-2, 4-8, 19, 38-41, and 43 based upon 35 U.S.C. § 112, first paragraph. In the declaration, Dr. Michal Schwartz makes reference to a publication, Hauben et al. Proc Natl Acad Sci USA, 98: 15173-15178, 2001, in which all of the experiments were conducted either by him or under his supervision. Dr. Schwartz points out the experiment that bridges columns 1-2 on pg 15176, establishes that T cells directed against Nogo-A-derived peptide are neuroprotective when passively transferred into SPD rats. Although the experiments in the Hauben et al. reference indicate positive results after utilizing Nogo-A activated T cells, the declaration is not persuasive. Specifically, the reagents utilized in Hauben et al. were not disclosed in the specification of the instant application as originally filed and were not available in the prior art. Therefore, undue experimentation would still be required of the skilled artisan to determine what other NS-specific antigens could be used to activate T cells and reduce neuronal degeneration. Relevant literature teaches that about 200,000 distinct mRNA sequences are thought to be expressed in the brain alone (a component of the central nervous system) and that this diversity results from the greater number and variety of cell types in the brain as compared to cells in the more homogeneous body tissues (pg 49, ¶ 1; Schwartz, J., "Synthesis and

Trafficking of Neuronal Proteins", Principles of Neural Science, Connecticut: Appleton and Lange, 1991, pages 49-65). Schwartz states that the three membrane systems which constitute separate compartments within the neuron are made up of different proteins and serve separate functions within the cell (pg 50). Schwartz also continues to explain that a nerve cell makes three general classes of proteins: cystolic, nuclear/mitochondrial/peroxisomal, and cell membrane/secretory (pg 50-55). Therefore, due to the large quantity of proteins/antigens present in the central nervous system alone, the present invention is also unpredictable and complex wherein one skilled in the art may not necessarily reduce any kind of neuronal degeneration in the central nervous system or peripheral nervous system comprising administering *all types of NS-specific activated T cells*.

Additionally, undue experimentation would also be required of one skilled in the art to provide T cells for future use by obtaining T cells from a human individual who is not suffering from an injury involving neuronal degeneration and activating said T cells against at least one nervous system antigen out of thousands of possible antigens as mentioned above.

(ii) At the bottom of page 11 of the Response, Applicant argues that in paragraph 7 of the declaration of Dr. Schwartz, the active vaccination with MOG (as described in Example 8.2 of the specification) would cause one of ordinary skill in the art to expect that the concomitant passive vaccination with MOG-activated T cells would also be neuroprotective.

Applicant's arguments and the declaration of Dr. Michal Schwartz are not found to be persuasive. Example 8.1-8.2 of the specification (pg 68-69) refers to the administration of a MOG *protein* to rats, rather than the elected invention of NS-specific activated T cells.

Furthermore, although this example does not exemplify the claimed invention, the administration of MOG is not shown in the specification to activate T cells. Undue experimentation would be required of the skilled artisan to sensitize T cells to every nervous system antigen, including MOG, and administer the cells to an individual to reduce any type of neuronal degeneration. One skilled in the art would not be able to predict that passive vaccination with MOG-activated T cells would be neuroprotective because, as mentioned above in part (i) above, proteins related to nerve cells alone are structurally and functionally diverse. MOG-activated T cells may not produce the same results *in vivo* as the MBP-activated T cells disclosed in the instant specification.

(iii) The specification teaches that "a catastrophic consequence of central nervous system injury is that the primary damage is often compounded by the gradual secondary loss of adjacent neurons that apparently were undamaged, or only marginally damaged by the initial injury"(pg 3, last ¶). The specification also discloses that "neurons in the central nervous system do not undergo spontaneous regeneration following an injury" (pg 4, ¶ 2). As echoed by Jackowski, it is well known in this unpredictable art that regeneration does not occur in the CNS either because processes fail to grow the necessary distance, they are in competition with other nearby neuronal processes not derived from the affected nerve, astrocytic scarring blocks axonal elongation, or because of misdirected axonal growth (e.g., see Jackowski, Brit J Neurosurgery 9: 303-317, 1995; specifically pgs. 309-310 and pg. 305, last ¶). Accordingly, because of the lack of guidance provided by the specification as to how one can rescue dead or dying cells instantaneously affected, for example, by a head injury, there is no nexus that merely

administering NS-specific T cells to an individual in need thereof can reasonably be extrapolated to successfully treat any human subject experiencing *"primary"* neuronal degeneration, as claimed, without undue experimentation to determine such. However, examples in the specification of the instant application indicate that MBP-specific T cells reduce *secondary* neuronal degeneration caused by spinal cord injury or blunt trauma (see pg 53-54; pg 60-64).

Proper analysis of the Wands factors was provided in a previous Office Action. Due to the large quantity of experimentation necessary to generate all possible NS-specific activated T cells and reduce "primary" neuronal degeneration by administering all possible NS-specific activated T, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the unpredictability of the effects of administering any NS-specific T cells to an individual, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Claim Rejections - 35 USC § 112

9. Claims 38-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claims 38-39 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the administration of NS-specific activated T cells. A similar rejection was made to claims 38-39 as set forth at pg 9 of the previous Office Action (Paper No. 17, 30 July 2002).

Applicant's arguments (Paper No. 20, 30 December 2002), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

At page 14 of the Response, Applicant argues that the specification states that the effects of CNS or PNS injury or disease that result in NS degeneration can be prevented or inhibited by administering an NS-specific antigen or a peptide derived therefrom or a derivative thereof so as to activate T cells in vivo to produce a population of T cells that accumulate at the site of injury or disease of the CNS or PNS. Applicant contends that *in vitro* activation of the T cells and administration thereof is not an essential step to cause a population of T cells to accumulate at the site of injury or disease. Applicant argues that claim 38 is intended to be generic to either *in vivo* or *in vitro* activation of the T cells. Applicant submits that the administration of activated T cells is not an essential step.

Specifically, Applicant's arguments have been fully considered but are not found to be persuasive because it is inappropriate to read limitations in the specification into the claims. The claims must independently define the invention for which patent protection is sought. Therefore, the claims are still rejected as being indefinite because the claims do not recite a step which causes the NS-specific activated T cells to accumulate at the site of neuronal degeneration. It is noted to Applicant that claims 38-39 have been examined to the extent that they read upon the elected group of administration of NS-specific activated T cells.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

Elyabeth C. Kemmerer

BEB
Art Unit 1647
March 18, 2003